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Association of Treatment with Remdesivir and 30-day Hospital Readmissions in Patients Hospitalized with COVID-19

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Short Title: Association of Remdesivir and Hospital Readmission

Abstract

Background: Since the beginning of COVID-19 pandemic, there has been a widespread use of remdesivir in adults and children. There is little known information about remdesivir's role in reducing 30-day readmissions after hospitalization with COVID-19. This study aimed to determine whether treatment with remdesivir was associated with reduced risk of 30-day readmission after index hospitalization with COVID-19.

Methods: The study was a multi-center cohort study in Rhode Island, USA. Patients included all adults that were discharged after hospital treatment for COVID-19 between April 1st and December 31st, 2020. The main study outcomes were length of hospital stay, 30-day readmission, and post-discharge 30 days mortality.

Results: A total of 2,062 patients (2,279 hospitalizations) were included in the analytic sample. Patients were less likely to be readmitted within 30 days if they received remdesivir relative to not receiving remdesivir; associations were strongest for those with mild disease (RR: 0.31; 95% CI: 0.13,0.75). Remdesivir treatment was associated with reduction in all-cause mortality (HR: 0.65; 95% CI: 0.49,0.85) and an increase in length of stay (estimated average increase of 3.27 days; 95% CI: 2.11,4.44). Limitation: Unmeasured factors such as time-to-treatment and severity of disease prior to initiation of remdesivir.

Conclusions: Remdesivir may be an effective strategy for reducing progression to severe COVID-19 disease and limiting morbidity associated with readmission to hospital. Larger prospective studies are justified to study the role of remdesivir in mild or early COVID-19 with high risk of disease progression and readmission to hospital within 30 days.

MeSH terms: remdesivir, COVID-19 hospitalization, COVID-19 disease, hospital readmission

Introduction

The pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has recorded more than 181 million global cases and 3.9 million deaths as of June, 2021.[1] In the United States 2.2 million hospital admissions for coronavirus disease 2019 (COVID-19), the syndrome caused by SARS-CoV-2, have occurred from August 1st, 2020 to June 26, 2021.[1] In-hospital mortality ranges from 0.3-13.3% by age group and increases with age.[1] Hospital readmission rates amongst survivors are not readily available but have been reported between 4-20% within 60 days of discharge.[2-4]

Currently remdesivir, a nucleotide analogue prodrug, is approved by the US Food and Drug Administration (FDA) for the treatment of hospitalized patients with COVID-19. Guidelines from the US National Institute of Health (NIH) recommend use of remdesivir for patients hospitalized with COVID-19 and requiring oxygen (Grade BIIa).[5] There are insufficient data to recommend use of remdesivir for the treatment of hospitalized patients not requiring supplemental oxygen. The guidelines are currently limited by the low number of randomized trials and perceived low mortality and morbidity rates in this subgroup of hospitalized patients.[6,7] Additionally, dexamethasone, a corticosteroid, is recommended for the treatment of patients with moderate and severe COVID-19 disease requiring supplemental oxygen, including high-flow devices, non-invasive ventilation and mechanical ventilation.[5] Antibiotic, anticoagulant, and diuretic medications are other therapeutic options commonly employed in the treatment of COVID-19 and related complications.

Little is known about relationships between pharmacological treatments of COVID-19 and post-discharge outcomes. Reasons for readmission to hospital after COVID-19 may include underlying co-morbid disorders, social determinants of health such as access to housing and access to health care, as well as susceptibility to progression of COVID-19.[8,9] We hypothesized that administration of remdesivir to hospitalized patients with mild COVID-10 disease may result in decreased viral replication and ultimately less morbidity as represented by hospital readmission. The aim of the study was to examine the association between readmission and remdesivir using inverse-probability of treatment weights in a cohort of patients admitted to hospital during the COVID-19 pandemic at a large hospital system in Rhode Island from April to December 2020.

Methods

Study setting and population. From April 1, 2020, to December 31, 2020, there were 2,557 COVID-19 related hospital admissions within the Lifespan network (Rhode Island Hospital, The Miriam Hospital, Newport Hospital) in 2,230 unique patients aged 18 years and older. All patients identified tested positive for presence of SARS-CoV-2 coronavirus via nasopharyngeal swab or serum serology testing. Serum serology was utilized for diagnosis when patients were admitted with clinical presentation consistent with COVID-19 but had negative polymerase chain reaction testing for SARS-CoV-2 by nasopharyngeal swab. The combined Lifespan Institutional Review Board approved the study protocol. Details regarding the clinical course, rehospitalizations, and/or deaths were abstracted from the electronic health records (EHR). Our analytic sample was restricted to the 2,279 hospitalizations (N=2,062 patients) with complete data on sociodemographic and clinical covariates of interest. In this historical cohort study, for each hospitalization a given patient was followed from admission to 30 days post discharge.

Outcome Measures

Outcome measures of interest included length of hospital stay, 30-day readmission, and post-discharge 30-day mortality. Patients who died prior to discharge were classified as dying at 0 days post discharge.

Statistical Analysis

All analyses were conducted using Stata version 16.1 (StataCorp, College Station, Texas). Characteristics and outcome events of patients treated with and without remdesivir are reported as column percentages or mean and standard deviation, as appropriate. Subsequent marginal structural models regressing outcomes of interest on remdesivir use were weighted using inverse-probability of treatment weights (IPTW) to address confounding by indication (i.e., non-randomized treatment allocation) and inverse-probability of censoring weights (IPCW) to address selective survival.

Inverse-probability of treatment weights (IPTW)

The propensity score (PS) for treatment with remdesivir for each patient was estimated using logistic regression, which modeled the probability of being treated with remdesivir, compared to not being treated with remdesivir, using patient gender, race, ethnicity, language, age, insurance type, smoking status, medical history (yes/no for presence of particular medical diagnoses in the EHR), as well as the results of laboratory values (ALT, AST, eGFR) and vital signs (hypotension, hypoxia, fever, tachycardia, respiration rate above 30 measured) within 24 hours of index admission. Variables for the IPTW models were chosen by identifying potential confounders as well as causes of readmission, extended length of stay, and death that are not in the causal pathway using directed-acyclic graphs (DAGs). Weights were stabilized using the marginal probability of being treated with remdesivir (probability of being treated with remdesivir/ being treated with remdesivir, given their covariates [i.e., PS]). The sample created using IPTW assumes that the distribution of baseline characteristics is independent of treatment assignment.

Inverse-probability of censoring weights (IPCW)

The propensity score (PS) for dying before or within 30 days of discharge for each patient was estimated using logistic regression, which modeled the probability of dying before or within 30 days of discharge, compared to still being alive 30 days after discharge. Included variables were again selected with the use of DAGs. This model included the same covariates used in the development of IPTW as well as treatment type (remdesivir, antibiotics, steroids, anticoagulants, diuretics), maximum/most extreme laboratory values during admission (AST, WBC, lymphocytes, albumin, ALT, eGFR), the maximum amount of respiratory support, and vital sign abnormalities within 24 hours of discharge (hypotension, hypoxia, fever, tachycardia, respiration rate above 30 measured).

Marginal Structural Models

To estimate the treatment effect of receiving remdesivir relative to not receiving remdesivir on length of stay and 30 days readmission, generalized linear models were weighted by the product of IPTW and IPCW for each hospitalization truncated at the 5th and 95th percentiles. Likewise, marginal structural Cox models were used to estimate the treatment effect of receiving remdesivir relative to not receiving remdesivir on 30-day survival, weighted by the stabilized IPTW. All models accounted for clustering at the patient level.

Stratified-Analyses

A priori we hypothesized the potential for the greatest benefit to be conferred for patients treated with remdesivir whom had mild COVID-19 related disease. Patients were categorized as “mild” during their hospitalization if they did not require supplemental oxygen. Alternatively, those who required 0.5-6Lpm maximum oxygen support were categorized as “moderate” and those who required 6.5Lpm or more, including high flow, non-invasive ventilation, and mechanical ventilation, were classified as “severe”.

Sensitivity analyses

In separate alternative model specifications, we estimate the treatment effect of receiving antibiotics, steroids, diuretics, and anticoagulants on length of stay, readmission within 30 days, and 30-day survival.

Results

Of the 752 hospitalized patients who received remdesivir (N=758 hospitalizations), 742 (N=748 hospitalizations) were included in this analytic sample. Likewise, of the 1,538 patients who did not receive remdesivir (N=1,799 hospitalizations), 1,369 (N=1,531 hospitalizations) were included in this analytic sample. Those included in the analytic sample tended to have a longer length of stay (median: 5 days [IQR: 3 days, 10 days] vs median 3 days [IQR: 1 day, 7 days]. Table 1 summarizes the characteristics of the 2,062 patients (2,279 hospitalizations) included in the analytic sample stratified by remdesivir treatment status. Remdesivir treatment was disproportionately given to those who were older, men, white, and with admission vitals indication respiration rate >30 and higher CRP values. Additionally, patients treated with remdesivir disproportionately required some degree of respiratory support at some point during their hospitalization. Those treated with remdesivir tended to have a longer length of stay but a smaller proportion were admitted within 30 days of discharge. Table 2 further summarizes characteristics by COVID-19 symptoms severity. Patients with mild symptoms were disproportionately younger and BIPOC, while those with more severe symptoms were disproportionately older, white, and with a greater number of comorbid health conditions.

Sampling Weights Distribution and Balance

Truncated IPCW, IPTW, and the combined weight had a mean ± standard deviation of 0.80±0.22, 0.96±0.42, and 0.76±0.40, respectively (Supplemental Table A1). The characteristics of the 2,062 patients hospitalized with COVID-19 (2,279 hospitalizations) stratified by

remdesivir treatment status after applying inverse probability of treatment weights are displayed in Supplemental Table A2 and demonstrate greater balance relative to characteristics displayed in Table 1 particularly as they pertain to labs and vitals measured around the time of admission.

Marginal Structural Models

Association of treatment with remdesivir with length of stay, 30-day readmission, and all-cause mortality in 2,062 patients hospitalized with COVID-19 (2,279 hospitalizations) are displayed in Table 3.

Length of Stay

Overall, being treated with remdesivir was associated with a 3.27 day (95%CI: 2.11,4.44) increase in length of stay on average relative to not being treated with remdesivir. This finding was most pronounced for those with severe COVID-19 symptoms (β: 6.70 days; 95%CI: 0.47,12.92) while those with mild and moderate symptoms had a fairly negligible increases in length of stay.

Readmission within 30 days

Overall, being treated with remdesivir was associated with a 19% decrease in risk of 30-day readmission (95%: 0.59,1.13). Patients with mild disease were 69% less likely to be readmitted within 30 days had they received remdesivir relative to not receiving remdesivir (RR: 0.31; 95% CI: 0.13,0.75).

30-day All-Cause Mortality

Overall, being treated with remdesivir was associated with a 35% decrease in risk of dying in the 30-days following discharge (HR: 0.65; 95%:0.49,0.85).

Sensitivity Analyses

Supplemental Tables A3-A6 display the results of sensitivity analyses employing steroids, antibiotics, anticoagulants, and diuretics in place of remdesivir as the treatment, respectively. Generally, all alternative models yielded comparable or worse health outcomes. Treatment with corticosteroids was associated with increased risk of readmission within 30 days and treatment with antibiotics was associated with increased length of stay as well as increased risk of dying within 30 days following discharge.

Discussion

Treatment with remdesivir has been shown to improve disease severity and shorten duration of symptoms in patients with moderate to severe COVID-19 disease.[10,11] The benefits of treatment with remdesivir in mild disease severity have not been established. In our retrospective multicenter analysis within a large hospital network, receipt of remdesivir was associated with lower likelihood of 30-day readmission after hospitalization; associations were strongest for those with mild COVID-19, defined as hospitalized but not requiring supplemental oxygen. Additional COVID-19 treatments investigated including corticosteroids, antibiotics, diuretics and anti-coagulants were not associated with a reduction of hospital readmission rates. We also observed improved overall survival and increased hospital length of stay associated with remdesivir treatment. Our study population represents a broad range of real-world patients presenting to hospital in the period encompassing the “spring” and “fall” 2020 COVID-19 case number surges in Rhode Island, USA. While non-randomized treatment allocation can be a significant source of bias in observational assessments of different treatments, we leveraged rich sociodemographic and clinical data to construct IPTWs and additionally construct IPCWs to reduce the impact of confounding by indication and selective survival on our estimates, respectively. This is the first report on hospital readmissions in a large cohort of patients treated with remdesivir, likely owing to the early availability of remdesivir in Rhode Island.

Hospital readmission rates after hospitalization for COVID-19 range between 4-20%.[2] Between 30-80% of readmitted patients return to hospital with a primary diagnosis of COVID-19 or related adverse event including sepsis, pneumonia, hypoxic respiratory failure, and thromboembolism.[3,4] Other reasons for hospital readmission include exacerbation of underlying conditions such as congestive heart failure and pulmonary disease, and a decline in overall functional status. Mortality upon readmission ranges up to 23%.[4]

Remdesivir, a nucleotide analogue prodrug, acts as a viral RNA-dependent RNA polymerase inhibitor, targeting the viral genome replication process.[12,13] Treatment with remdesivir early in the clinical course of COVID-19 may limit SARS-CoV-2 viral replication and prevent progression to more severe disease. Studying the effects of remdesivir presents a conundrum which is likely related to the disease biology of SARS-CoV-2 and COVID-19.[14] Remdesivir may be a treatment agent for COVID-19 which is most effective in mild to moderate disease, and therefore may not exhibit a mortality reduction due to the lower overall mortality rates in this sub-population of patients. Our findings suggest that patients who develop severe disease may also benefit from remdesivir's anti-viral effects as is suggested by current guidelines recommending treatment with remdesivir in this population.[5,14,15] Remdesivir has not been shown to improve overall mortality across several randomized studies, but we are encouraged to see an association with mortality reduction in this real-world data set. Evidence demonstrating a reduction of co-morbid outcomes such as reduced 30-day hospital readmission rates in this analysis, may form the basis for ongoing clinical use of remdesivir in hospitalized patients with mild COVID-19 disease.[16]

In studies reporting on rates of hospital readmissions after COVID-19 hospitalization, treatments included including hydroxychloroquine, lopinavir/ritonavir, corticosteroids, anticoagulants and remdesivir.[4,17-20] A study with a small number of patients treated with remdesivir reported 0/22 patients readmitted within 30 days.[4] By comparison, other treatments such as hydroxychloroquine and corticosteroids, were not associated with a reduction in hospital readmissions.[4] A prospective randomized trial evaluating the treatment effect of remdesivir conducted in outpatients with early COVID-19 disease revealed a decrease in hospital admissions in the remdesivir arm supporting the idea that anti-viral therapy for COVID-19 has an active role in clinical management but likely heavily depends upon timing within the disease course. In our analysis commonly used treatments for COVID-19 such as corticosteroids, anticoagulants, antibiotics and diuretic medications were not associated with reduced readmissions or in-hospital mortality.

Propensity score matching (PSM) and inverse probability of treatment weighting (IPTW) are increasingly popular methods used to address confounding by indication.[21] IPTW aims to achieve a balanced distribution of confounders across treatment groups and thereby achieve a more robust baseline for comparison. An estimated propensity score reflects the probability of treatment assignment conditional on a patient's measured baseline characteristics, which in this analysis included a broad range of underlying diagnoses, social factors, clinical indicators

including vital signs and laboratory studies, and in-hospital complications. An additional adjustment was performed to account for survivorship bias.

Remdesivir may be an effective strategy for reducing progression to severe COVID-19 disease and limiting morbidity associated with readmission to hospital. Further prospective studies will be required to confirm this finding to help revise current guidelines even as we grapple with resurgence of cases of COVID-19. Although not currently included in guidelines for treatment of hospitalized patients with mild COVID-19, remdesivir should be considered for those patients with defined risk factors for disease progression and readmission to hospital within 30 days.

Our study has important limitations. Treatment with remdesivir was not randomized and there are known clinical factors that dictate differential allocation of treatment. In attempts to mitigate the contribution of confounding by indication, we leveraged available data on underlying diagnoses, social factors, and clinical indicators – as measured and recorded in the electronic health record – to estimate and incorporate probability of treatment assignment as IPTWs. IPTW – as with other techniques employed for confounding control – can only balance factors that are measured. Unmeasured factors, such as time-to-treatment with remdesivir and timing of maximum respiratory support in relation to remdesivir treatment, may play a role in the analysis.

Conclusions

We observed an association between reduction in likelihood of hospital readmission in patients with mild COVID-19 who were treated with remdesivir. These results provide evidence that augments the case for use of remdesivir in patients hospitalized with mild (early) COVID-19 disease, particularly in patients with risk factors for progression to severe disease as recommended by treatment guidelines. Additionally, we observed an association of overall mortality reduction and remdesivir treatment in this real-world analysis. Due to the nonrandomized nature of our analysis, additional study of the treatment effect of remdesivir in COVID-19 is required.

Conflicts of Interest

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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Table 1. Characteristics of 2,062 patients hospitalized with COVID-19 (2,279 hospitalizations) stratified by Remdesivir treatment status, Lifespan Network February 2020 – December 2020

	No Remdesivir (N=1531 Hospitalizations)	Remdesivir (N=748 Hospitalizations)	Total (N=2279 Hospitalizations)
	Col % or Mean (Std. Dev)		
Gender			
Women	48.4	42.4	46.4
Men	51.6	57.6	53.6
Age (years)	63.0 (18.4)	64.2 (16.7)	63.4 (17.9)
Race			
Asian	1.7	1.2	1.5
Black	16.9	13.1	15.6
NHOPI	0.5	0.4	0.4
Other	29.4	29.3	29.5
White	50.7	54.5	51.9
Hispanic or Latino/a/x Ethnicity	32.8	33.4	33.1
Not English Speaking	33.0	33.8	33.2
Insurance Type			
Private	56.1	55.4	55.9
Self-pay	4.6	5.8	5.0
Medicaid	7.8	7.0	7.6
Medicare	31.5	31.8	31.6
Medical History			
Current or Former Tobacco Use	34.8	35.8	35.2
Cardiac	44.9	41,8	43,8
Hypertension	61.7	63.5	62.3
Diabetes	40.7	42.5	41.3
Obesity	5.4	6.2	5.6
Vascular Disease	3.0	4.3	3.5
Endocrine disorder	3.3	2.0	2.9
Pulmonary	37.6	40.1	38.4
Venous Thromboembolism	11.7	13.6	12.3
Neuro	26.1	20.2	24.2
CKD & Dialysis	23.6	16.0	21.1
Malignancy	17.7	15.8	17.1
Hematologic Conditions	27.6	22.6	26.0
Gastrointestinal	4.3	2.0	3.5
Immunocompromised	15.0	14.2	14.7
Within 24 hours of admission			
RR>30	29.1	49.9	36.0
AST	48.8 (127.7)	42.7 (28.4)	46.8 (106.0)
ALT	37.8 (103.6)	34.6 (31.6)	36.7 (86.8)
CRP	83.8 (82.1)	110.2 (84.9)	93.5 (84.1)
D-dimer	1233.9 (4261.8)	1125.9 (4002.1)	1193.6 (4166.2)
eGFR	49.4 (17.3)	54.4 (12.1)	51.0 (16.0)
Max Respiratory Support			
None	47.1	11.4	35.3
<6L	30.0	43.7	34.5
6-14.99L	4.1	8.6	5.5
15-80L	4.5	10.2	6.4
BiPAP or CPAP	5.7	14.2	8.5
Ventilator	8.8	12.0	9.8
Outcome			
Neither Readmitted or deceased within 30 days	76.9	79.9	77.9
Readmitted within 30 days	11.8	8.3	10.6
Deceased within 30 days	11.4	11.8	11.5

Table 2. Characteristics of 2,062 patients hospitalized with COVID-19 (2,279 hospitalizations) stratified by symptom severity, Lifespan Network February 2020 – December 2020

	Mild (N=806 Hospitalizations)	Moderate (N=846 Hospitalizations)	Severe (N=627 Hospitalizations)
	Col % or Mean (Std. Dev)		
Gender			
Women	48.9	48.4	40.7
Men	51.1	51.7	59.3
Age (years)	60.4 (18.7)	64.0 (17.7)	66.5 (16.2)
Race			
Asian	2.0	1.3	1.3
Black	16.4	16.1	14.3
NHOPI	0.1	0.5	0.8
Other	34.4	26.6	26.6
White	46.4	54.3	56.0
Hispanic Latino/a/x Ethnicity	38.2	30.1	30.1
Not English Speaking	35.6	32.0	31.9
Insurance Type			
Private	59.2	57.8	49.1
Self-pay	5.8	5.2	3.5
Medicaid	8.2	6.2	8.6
Medicare	26.8	30.9	38.9
Medical History			
Current or Former Tobacco Use	32.6	33.8	40.3
Cardiac	34.1	40.4	61.2
Hypertension	61.5	61.7	64.0
Diabetes	38.2	39.0	48.4
Obesity	3.7	6.6	6.7
Vascular Disease	2.6	3.0	5.1
Endocrine disorder	1.1	2.1	6.1
Pulmonary	28.2	31.7	60.5
Venous Thromboembolism	8.4	12.1	17.7
Neuro	22.1	21.3	30.7
CKD & Dialysis	17.5	20.7	26.3
Malignancy	17.3	18.0	15.8
Hematologic Conditions	19.4	19.7	42.8
Gastrointestinal	3.5	2.0	5.7
Immunocompromised	11.2	13.0	21.7
Within 24 hours of admission			
RR>30	10.3	27.7	80.1
AST	40.6 (91.8)	45.5 (85.4)	56.5 (141.7)
ALT	34.2 (70.0)	35.2 (46.7)	42.0 (135.0)
CRP	56.7 (65.6)	94.3 (75.8)	134.5 (94.5)
D-dimer	577.4 (1461.6)	917.4 (2939.7)	2215.1 (6598.5)
eGFR	53.2 (14.2)	51.4 (16.2)	47.8 (17.2)
Treatment			
Remdesivir	10.6	42.4	48.4
Antibiotics	38.3	52.0	83.3
Diuretics	12.9	24.1	73.6
Steroids	22.2	45.4	61.5
Anticoagulants	17.5	24.0	63.5
Outcome			
Neither Readmitted or deceased within 30 days	85.3	87.2	55.9
Readmitted within 30 days	13.0	9.6	8.9
Deceased within 30 days	1.7	3.2	35.2

1. Did not require oxygen
2. Required 0.5-6Lpm

3. Required 6.5Lpm or more, including high flow, non-invasive ventilation, and mechanical ventilation

Table 3. Association of treatment with Remdesivir with length of stay, 30-day readmission, and all-cause mortality in 2,062 patients hospitalized with COVID-19 (N=2,279 admissions), Lifespan Network February 2020 – December 2020

Patient Group	**Total**	**Num not on Remdesivir**	**Num on Remdesivir**	Length of Stay (days) β (95%CI)[1]	Readmission within 30 days of discharge RR (95% CI)[1]	All-Cause Mortality (HR 95% CI)[2]
All	2,279	1,531	748	3.27 (2.11,4.44)	0.81 (0.59,1.13)	0.65 (0.49,0.85)
Mild[3]	806	721	85	2.03 (0.66,3.39)	0.31 (0.13,0.75)	0.45 (0.12,1.65)
Moderate[4]	846	487	359	1.49 (-0.06,3.05)	0.77 (0.45,1.32)	0.40 (0.14,1.22)
Severe[5]	627	323	304	6.70 (0.47,12.92)	0.70 (0.38,1.28)	0.49 (0.33,0.73)

1. Generalized linear models with IPCW & IPTW weights to account for differential treatment assignment and survival. Models additionally control for month of admission and whether or not respiration rate was >30 within 24 hours of admission.
2. Cox proportional hazards model with IPTW weights to account for differential treatment assignment. Models additionally control for month of admission and whether or not respiration rate was >30 within 24 hours of admission.
3. Did not require oxygen
4. Required 0.5-6Lpm
5. Required 6.5Lpm or more, including high flow, non-invasive ventilation, and mechanical ventilation